REMARKS

After entry of this amendment, claims 1, 3-5, 7-33, 35-36 and 38-45 are pending.

35 U.S.C. § 112 Rejections

Further reconsideration is respectfully requested of the rejection of claims 1, 3-33 and 35-45 under 35 U.S.C. § 112, first paragraph as failing to comply with the enablement requirement. As explained in Amendment B, applicant respectfully maintains that the pending claims are fully enabled. To expedite prosecution, the claims have been amended to recite a method for "preventing or reducing the incidence of ototoxicity" in a patient undergoing treatment with either an anti-tumor platinum-coordination compound or an aminoglycoside antibiotic. While the Office states that the "[i]t is not seen from the data in the specification that the compound of the claims can be used to treat ototoxicity,"[1] applicant respectfully submits that the present amendments overcome this rejection and the amended claims satisfy the 35 U.S.C. § 112.

Further, the Office asserts that "a preventative measure has not yet been established somewhat in light of the issues concerning delivery of active agents."[2] The Office describes the delivery methods of other protective agents as impractical. However, delivery of the claimed otoprotective agents is not impractical; particularly, D-methionine can be administered parenterally, orally, and to the round window membrane and is known to be safe for human administration over a wide range of dosages. Also, because a person of skill in the art would know how to use the invention as described in human patients and the instant application shows otoprotection in animals, the instant claims satisfy the enablement requirement of 35 U.S.C. § 112.

[1] Page 5 of the Office action dated April 19, 2006.

[2] Page 5 of the Office action dated April 19, 2006.

35 U.S.C. § 103 Rejections Over Kowbata et al. in view of Deegan et al. and Ormond et al.

Reconsideration is respectfully requested of the rejection of claims 1, 3-5, 7-33, 35-36, and 38-45 as unpatentable over Kowbata et al. (U.S. 5,466,678) in view of Deegan et al. and further in view of Ormond et al. under 35 U.S.C. § 103(a). Applicant respectfully acknowledges the Office's finding that Kowbata et al. does not anticipate the pending claims. However, the April 19, 2006 Office action rejects the claims over Kowbata et al. on the basis of obviousness under §103. In this connection, the Office asserts that it

> would be inherent that S-adenosyl-L-methionine would prevent ototoxicity caused by a platinum complex compound, since a patient receiving a platinum complex compound is at risk for both nephrotoxicity and ototoxicity and using S-adenosyl-L-methionine to reduce nephrotoxicity would at the same time also prevent ototoxicity caused by the platinum complex compound.[3]

But this argument does not address §103. Instead, it merely repeats the grounds on which the Examiner has previously contended that Kowbata et al. anticipates the treatment of ototoxicity by administration of S-adenosyl-L-methionine.

Whether the Examiner's contention about the inherent effect of S-adenosyl-L-methionine is accurate or inaccurate has been rendered moot by the previous amendment which limited the claims so that they do not read on the administration of S-adenosyl-L-methionine. The issue now is whether it would have been obvious to treat cisplatin-induced ototoxicity by treatment with methionine derivatives other than S-adenosyl-L-methionine. What the inherent effect of S-adenosyl-L-methionine is or is not has nothing to do with that issue.

In resolving the obviousness issue, the inventors' disclosure cannot be used against her. With the benefit of applicant's disclosure, it is now obvious that methionine

[3] Page 3 of the Office action dated April 19, 2006.

and a number of methionine derivatives are effective against ototoxicity in patients receiving a platinum co-ordination compound. But that is not taught by Kowbata. Even if administration of S-adenosyl-L-methionine is inherently effective against ototoxicity, there is nothing in the Kowbata disclosure that recognizes this or in any way suggests it to one skilled in the art who is reading the Kowbata text. Much less is there any suggestion that the currently claimed treatment, which encompasses administration of other methionine derivatives but not S-adenosyl-L methionine , would have any effect on ototoxicity.

Inherency can, of course, be fatal to novelty of a claim that reads on what is inherent. But inherency as such has no relevance to obviousness of a claim that does not read on the inherent subject matter. As stated by the C.C.P.A in *In re Spormann*,

> [t]hat which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown.[4]

Kowbata et al. merely disclose that administration of S-adenosyl-L-methionine (SAMe) with cisplatin reduces the nephrotoxicity known to arise from cisplatin administration. The reference does not disclose nor suggest that SAMe or any other composition would inevitably be effective to protect against ototoxicity. The text of Kowbata contains no mention of ototoxicity. To the extent it has any relevance at all, the reference would have led a person of ordinary skill to believe that SAMe was only effective as a nephroprotectant. For example, Kowbata et al. state

> ...SAMe, when administered intravenously, concentrates specifically at the renal tissue, where it is converted through the process of transmethylation to S-adenosylhomocysteine...which in turn is converted to such compounds as homocysteine, cysteine and glutathione. It was also noted that there was no increase in the blood level of these SH-compounds after the SAMe administration.[5]

Also, the data in Table I of Example 4 shows a significant increase in SH compounds in the renal tissue, but not a significant increase in these compounds in the blood plasma.

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[4] *In re Spormann*, 150 U.S.P.Q. 449.
[5] See Kowbata et al. (U.S. Patent No. 5,466,678) at column 2, lines 41-48.

Generally, for a protectant compound to be effective against ototoxicity, it must reach the cochlea. Consequently, because the distribution studies showed SAMe did not significantly increase the blood plasma levels of SH compounds, it would not have been obvious to a person of ordinary skill upon a reading of the Kowbata reference that SAMe would be an effective protectant for ototoxicity caused by cisplatin exposure.

Furthermore, if it would not have been obvious that SAMe was an effective otoprotectant, it certainly would not have been obvious from the Kowbata reference that methionine was an effective otoprotectant. There is much evidence that different otoprotective agents have different therapeutic mechanisms and as such may or may not be effective for a specific mechanism of ototoxicity. This knowledge of the differences in mechanisms for different causes and otoprotective agents would not have led one of ordinary skill from the use of S-adenosyl-L-methionine as a nephroprotectant for cisplatin administration to the use of methionine as an otoprotectant for cisplatin exposure.

Deegan et al. generally describe the nephrotoxicity, cytotoxicity, and renal handling of a cisplatin-methionine complex. The Deegan reference discloses that when the cisplatin-methionine complex is administered, cisplatin-induced nephrotoxicity is not exhibited in Wistar rats. Also, Deegan et al. found that cisplatin is a substrate for the organic base transport system (evidenced by net renal secretion) while a cisplatin-methionine complex is not such a substrate (evidenced by secretion by filtration only). Deegan et al. also state that this function as a substrate for organic base transport system may be the determinant factor for nephrotoxicity.[6]

Further, Ormond et al. generally describe reduced nephrotoxicity of a cisplain-methionine complex and makes the observations that the reduced nephrotoxicity of the cisplatin-methionine complex as compared to cisplatin alone may be because the cisplatin-methionine complex is not being transported by the renal proximal tubule. Thus, Deegan and Ormond both describe the nephroprotective mechanism of

[6] Deegan et al., *Toxicology* **1994**, *89*, at page 12.

methionine as forming a complex with the cisplatin wherein this cisplatin-methionine complex is not handled by the kidneys in the same way as cisplatin alone.

While Deegan and Ormond may extend the teachings of Kowbata from S-adenosyl-L-methionine to methionine with respect to the treatment of nephrotoxicity, that is clearly all they do. Certainly neither Deegan nor Ormond includes any disclosure that could be construed as inherently affecting ototoxicity. The Examiner has made no such contention; and if were made, it could not be supported.

With regard to §103, Deegan and Ormond have nothing more to say about the treatment of ototoxicity than Kowbata et al. Three references which say nothing about ototoxicity cannot be combined to create a teaching that does. As described above, the Kowbata reference would not have led a person of ordinary skill to contemplate that SAMe or methionine could have an otoprotective effect. Similarly, the Deegan and Ormond references describe only the nephroprotectant and renal handling properties of a cisplatin-methionine complex. From an examination of these references, a person of ordinary skill would not have found the instant claims obvious without use of impermissible hindsight reconstruction using applicant's disclosure as a template. Therefore, claims 1, 3-5, 7-33, 35-36, and 38-45 are nonobvious and satisfy the requirements of 35 U.S.C. § 103(a).

Applicant submits that the present application is now in a condition for allowance and requests early allowance of the pending claims.

The Commissioner is hereby authorized to charge $60 for a one month extension of time. The Commissioner is hereby authorized to charge any under payment or credit any over payment to Deposit Account No. 19-1345.

Respectfully submitted,

Janet S. Hendrickson, Ph.D., Reg. No. 55,258
SENNIGER POWERS
One Metropolitan Square, 16th Floor
St. Louis, Missouri 63102
(314) 231-5400

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